

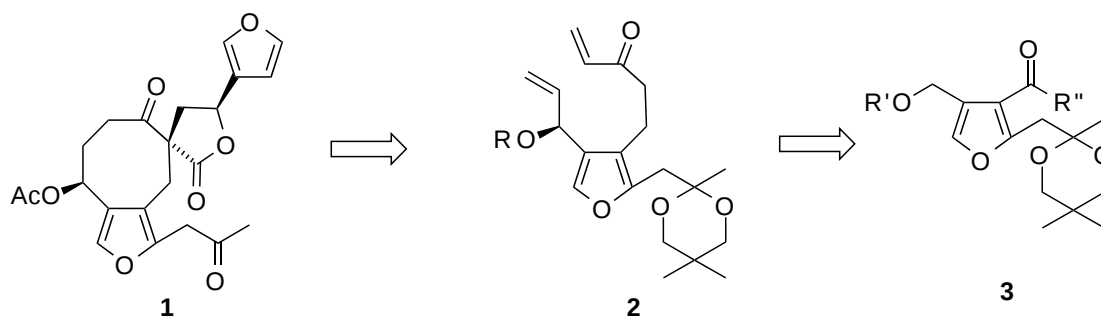
A REGIOSELECTIVE ROUTE TO 2,3,4-TRISUBSTITUTED FURANS[‡]

Ivan Efremov¹ and Leo A. Paquette*

Evans Chemical Laboratories, The Ohio State University, Columbus, OH 43210, USA

Abstract - Several potential routes to furans substituted with C-C bonds at the 2-, 3-, and 4- positions have been evaluated.

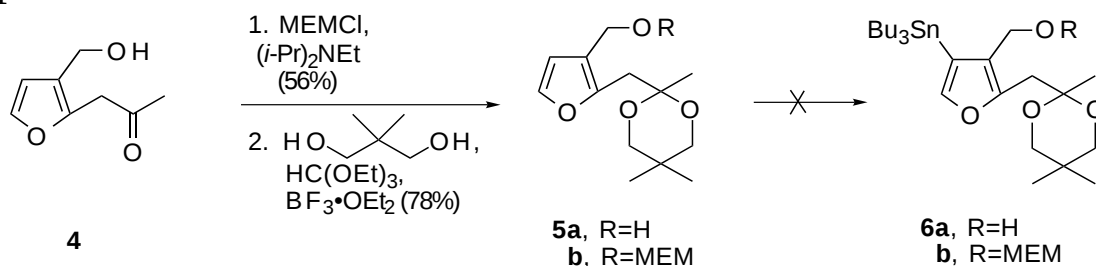
We have undertaken the goal of a total synthesis of the rearranged *neo*-clerodane diterpenoid teubrevin G (**1**).² The presence of a medium-sized ring and the pattern of connectivity of its stereogenic centers were considered to provide a proper setting for the implementation of ring closing metathesis involving **2**.³ This stratagem prompted consideration in turn of an efficient means for producing **3**. The complexities associated with the generation of monocyclic 2,3,4-trisubstituted furans are well known⁴⁻⁶ and are not to be taken lightly. Of the four potential synthetic pathways examined here, only one proved to be practical and amenable to scale-up. Knowledge of the potential awkwardness awaiting certain approaches should preclude redundancy regarding their possible future application in related contexts.



The first route began with the known hydroxy ketone (**4**).⁷ Formation of the MEM derivative (**5b**) was followed by ketalization with neopentyl glycol (Scheme 1). After numerous attempts to introduce a tributyltin substituent at C-4 as in **6a** or **6b** were to no avail,⁸ the focus was shifted to the possibility of C-2 stannylation, which was expected to occur more readily.⁵ To this end, aldehyde (**8**) was prepared by *O* → *C* silyl migration performed on the previously reported **7**⁹ (Scheme 2). Treatment of **8** with vinylmagnesium bromide delivered the carbinol in 77% yield and set into motion two functional group modification steps leading efficiently to **9**. This alcohol reacted with 2.2 equiv of *n*-butyllithium in THF at 0 °C followed by

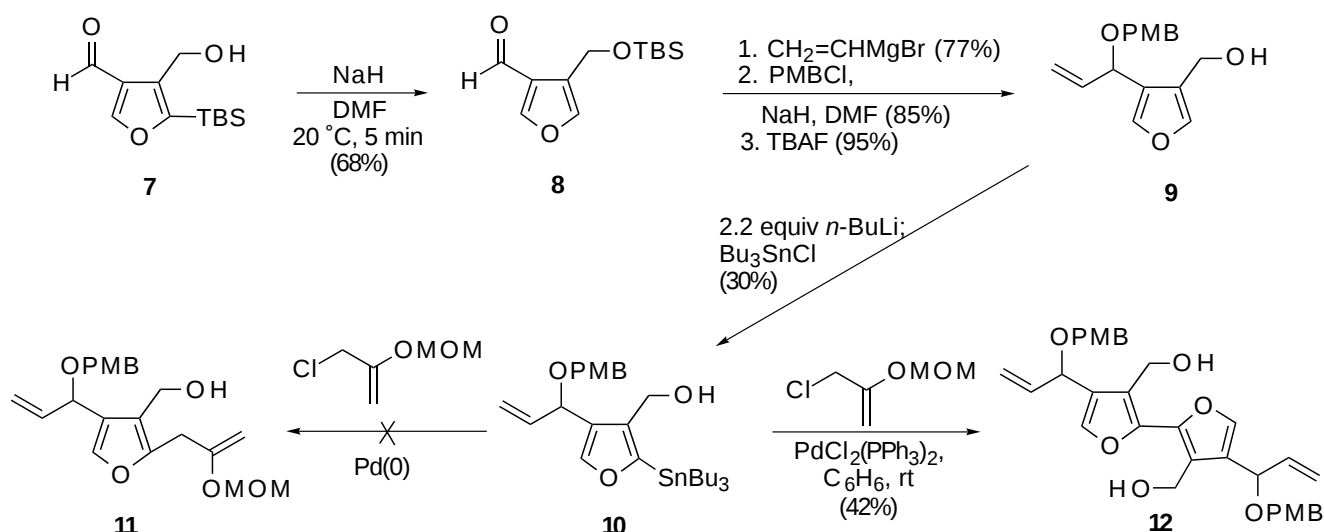
[‡]This paper is dedicated to Professor James Kutney as we celebrate his 70th birthday and his many substantive contributions to synthetic and bioorganic chemistry.

Scheme 1



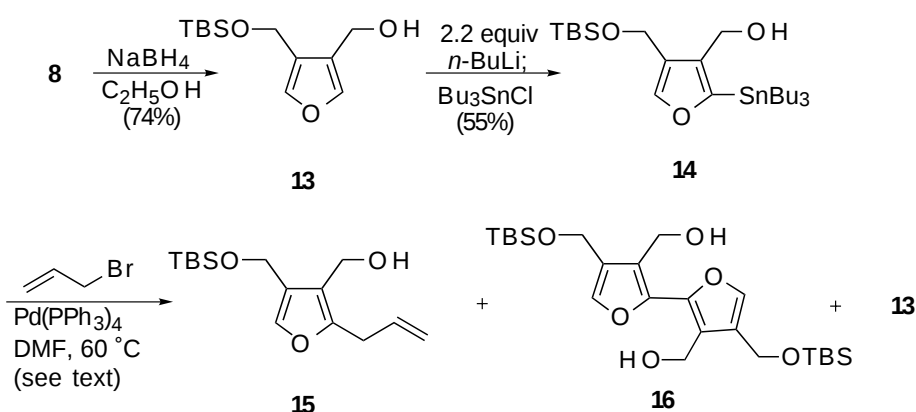
tri-*n*-butyltin chloride to afford **10**, but only in low (30%) yield. The difficulty in this instance conforms to the reported instability of 2-stannylated furans⁵ and manifests itself in the readiness with which **9** is regenerated upon the attempted purification of **10**. Beyond this, attempts to effect the palladium(0)-catalyzed coupling of **10** to 2-chloromethyl-3,5-dioxahex-1-ene gave rise not to the desired **11** but to the dimeric furan **12**.

Scheme 2



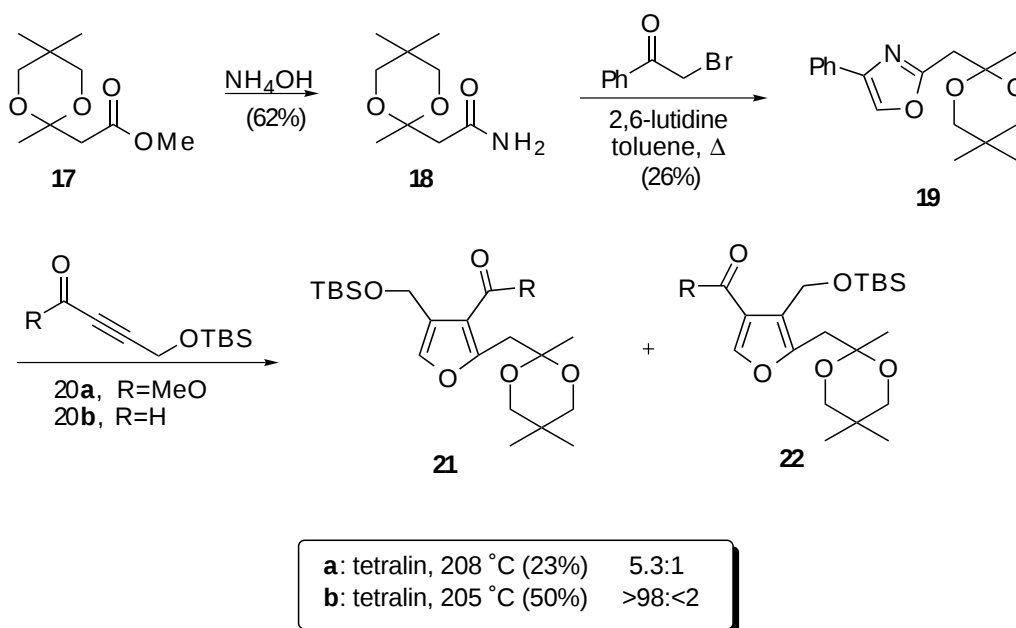
A comparable observation was made following the generation of **14** from **8**, and its palladium-mediated coupling to allyl bromide (Scheme 3). Although more elevated temperatures and the use of a polar aprotic solvent did serve to induce the formation of **15** (47%), simple destannylation (30% of **13**) and reductive coupling to give **16** (17%) were also operational.

Scheme 3

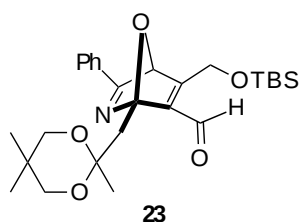


At this point consideration was given to the possibility of achieving appropriate thermal Diels-Alder cycloaddition-retrograde fragmentation between functionalized oxazoles and disubstituted alkynes. This ploy has seen extensive use when alkyne-tethered oxazoles are involved because structural constraints rule out the possible operation of competing regioselective pathways.¹⁰ Intermolecular [4+2] cycloadditions to unsymmetrical alkynes have been accorded much less attention¹¹ and potentially useful directive effects have not been elucidated.¹² Despite these concerns, we proceeded to transform methyl ester (**17**)¹³ into its amide in a step preliminary to formation of oxazole (**19**) (Scheme 4). Although formation of this heterocycle proceeded only with modest efficiency, the sequence proved easily scalable and the only chromatographic purification needed was readily accomplished. Heating ester (**20a**) with **19** in tetralin produced a 5.3:1 mixture of **21a** and **22a**. Yet more impressive and useful was the discovery that the involvement of aldehyde (**20b**) gave rise only to **21b** within our limits of detection.

Scheme 4



The substantial kinetic preference for formation of adduct (**23**) is noteworthy and suggests that steric and electronic effects are exploitable for the one-step regiocontrolled elaboration of 2,3,4-trisubstituted furans from oxazole precursors. The ease of access to **21** in this manner has proven to be particularly well suited to the expedient construction of **1**.³



ACKNOWLEDGMENT

We thank the Eli Lilly Company for financial support.

REFERENCES AND NOTES

1. Evans Graduate Fellow, 2000-2001.
2. B. Rodriguez, M. C. de la Torre, M. L. Jimeno, M. Bruno, C. Fazio, F. Piozzi, G. Savona, and A. Perales, *Tetrahedron*, 1995, **51**, 837.
3. I. Efremov and L. A. Paquette, *J. Am. Chem. Soc.*, 2000, **122**, 9324.
4. Review: X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. Tong, and H. N. C. Wong, *Tetrahedron*, 1998, **54**, 1955.
5. (a) E. Bures, P. G. Spinazzé, G. Beese, I. R. Hunt, C. Rogers, and B. A. Keay, *J. Org. Chem.*, 1997, **62**, 8741. (b) E. Bures, J. A. Nieman, S. Yu, P. G. Spinazzé, J.-L. J. Bontront, I. R. Hunt, A. Rauk, and B. A. Keay, *J. Org. Chem.*, 1997, **62**, 8750.
6. D. S. Brown and L. A. Paquette, *J. Org. Chem.*, 1992, **57**, 4512.
7. H. Glombik and W. Tochtermann, *Chem. Ber.*, 1983, **116**, 3366.
8. The inevitable major product was the result of opening of the dioxane ring.
9. R. E. Danso-Danquah, A. I. Scott, and D. Becker, *Tetrahedron*, 1993, **49**, 8195.
10. (a) B. Liu and A. Padwa, *Tetrahedron Lett.*, 1999, **40**, 1645. (b) P. A. Jacobi, T. A. Craig, D. G. Walker, B. A. Arrick, and R. F. Frechette, *J. Am. Chem. Soc.*, 1984, **106**, 5585. (c) P. A. Jacobi, D. and G. Walker, *J. Am. Chem. Soc.*, 1981, **103**, 4611. (d) P. A. Jacobi, D. G. Walker, and I. M. A. Odeh, *J. Org. Chem.*, 1981, **46**, 2065. (e) M. R. Iesce, F. Cermola, F. Giordano, R. Scarpati, and M. L. Graziano, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3295. (f) H. G. Selnick and L. M. Brookes, *Tetrahedron Lett.*, 1989, **30**, 6607.
11. (a) J. S. Yadav, M. Valluri, and A. V. R. Rao, *Tetrahedron Lett.*, 1994, **35**, 3609. (b) M. R. Iesce, F. Cermola, M. L. Graziano, and R. Scarpati, *J. Chem. Soc., Perkin Trans. 1*, 1994, 147.
12. Under ordinary circumstances, the oxazole functions as the electron-rich component and cycloaddition is considered to be governed by the HOMO of the oxazole and the LUMO of the dienophile. Inverse electron demand cycloadditions, although possible in theory, are very uncommon.
13. (a) L. O. Zamir, F. Sauriol, and C.-D. Nguyen, *Tetrahedron Lett.*, 1987, **28**, 3059. (b) T. H. Chan, M. A. Brook, and T. Chaly, *Synthesis*, 1983, 203.